High blood pressure at old age : The Leiden 85 plus study

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Chapter 8

Discussion

The hazardous effect of high blood pressure in people of middle age is a well known fact. Moreover, there is ample evidence from randomised clinical trials that favour treatment of high blood pressure. In contrast, there is a substantial amount of observational data that high blood pressure in elderly people above age 80 years is not associated with excess morbidity and or mortality. [1-6] In order to explain these apparent discrepancy, there must be a threshold beyond which treatment of hypertension does not provide benefit. However, it is difficult to understand the nature of this threshold, as age alone is not likely to explain for the paradox. After all, physiological systems are not bound to age. In this chapter the results of our research in the Leiden 85-plus Study are used to disentangle these seemingly contradictory findings in the very old.

The first objective of this thesis was to explore the association between high blood pressure, morbidity and mortality in a very old population. A diagnosis of hypertension at age 85 years was predictive of a 50% higher cardiovascular mortality during a five years follow-up period.[7] Remarkable, this increased risk was independent of the actual blood pressure and known cardiovascular diseases at age 85 years. No association was found between high systolic or diastolic blood pressure and mortality (total or cardiovascular). Unexpectedly, low systolic blood pressure concordant with a low diastolic blood pressure was associated with a two-fold increased risk of total mortality. These observations were irrespective of gender, current cardiovascular diseases and usage of antihypertensive drugs.
In chapter 3, the effect of blood pressure on renal function at old age was examined. [8] High systolic blood pressure was not associated with an accelerated decline of creatinine clearance. However, a decline in systolic and diastolic blood pressures over a five year period correlated with a 50% increased decline of creatinine clearance when compared to those with a stable blood pressure. Thus, at old age, high blood pressure was not a risk factor for renal dysfunction. In fact, a decrease of blood pressure at old age was associated with an increased decline of renal function.
In chapter 4 the relationship between baseline blood pressure and cognitive function later in life was examined across age groups from two independent population-based cohort studies. [9] Systolic and diastolic blood pressures were measured at baseline; cognitive function was assessed at the end of follow-up. In

the youngest age group (<65 years), systolic and diastolic blood pressures were not associated with cognitive function 11 years later. For persons aged 65-74 years, higher systolic and diastolic blood pressures at baseline were related to a decline in cognitive function 11 years later. In contrast, in older age (over 75 years) higher systolic and diastolic blood pressures were related with higher cognitive function 11 years later. This effect appeared to be strongest in the highest age group (85 years). Thus, the relation between baseline blood pressure levels and cognitive function later in life differs across age groups. High blood pressure increases the risk of cognitive impairment up to 75 years but may preserve cognitive function thereafter.

I conclude that high blood pressure is not related with excess mortality at age 85 years and over. High blood pressure has a preservative effect on creatinine clearance and finally high blood pressure seems to have a preservative effect on global cognition after age 75 years that is more pronounced after age 85 years. These observations point at a beneficial effect of high blood pressure in old age. The alternative hypothesis being that reversed causality is in play. Indeed, various chronic and cardiovascular diseases are associated with lower blood pressure and higher mortality rates. However, all the correlations reported here were corrected for the presence of cardiovascular and chronic diseases and the beneficial effects of high blood pressure still stand out. Moreover, reversed causality could explain for the relation between lower blood pressure and higher mortality risk, it is less likely to explain for the accelerated organ dysfunction that is described.

The second objective was to gain insight into the association between blood pressure and cardiac function at high age. Therefore, echocardiography examinations were performed in persons at 90 years of age. A first remarkable finding in the echocardiographic study was a high prevalence of significant mitral and aortic regurgitation. The combined prevalence of significant valvular disease was 70%.[Chapter 6] From a clinical perspective, it is noteworthy that our participants had little physical restrictions which points to limited impact of the valvular disease on the activities of daily living. As the echocardiograpic examinations were not thorough enough to make a reliable estimation of the cardiac output in the presence of severe valvular abnormalities, we have used only

the echocardiographic examinations of subjects who were free from significant valvular abnormalities to examine the association between blood pressure and cardiac output. Overall, the mean cardiac index was low, as was the mean stroke volume and both were significantly correlated with systolic blood pressure. [10] A lower systolic blood pressure correlated with lower cardiac index and lower stroke volume. Left ventricular end-diastolic and left ventricular end-systolic dimensions were within reference values and were not related to blood pressure. The mean left ventricular ejection fraction was normal and positively associated with blood pressure. The average E/A ratio was low also, indicating a high prevalence of diastolic dysfunction. Heart rates were significantly higher in participants with a lower stroke volume, compared to those with a higher stroke volume.

To examine the role of the autonomic nervous system associating with mortality, annually conducted electrocardiograms were studied. [11] A diminished parasympathetic dominance as measured with low heart rate variability did not show an association between mortality. Higher heart rate and the occurrences of ventricular extrasystoles, both presentations of excess sympathetic activity, were associated with an increased mortality. The dominance of the sympathetic nervous system could be either a result of an autonomous decrease in parasympathetic activity or a systemic adaptation to an underlying process.

Taken together I conclude that systolic function was preserved but there was a high prevalence of diastolic dysfunction and a decreased cardiac index. A lower systolic blood pressure was associated with a lower cardiac index and higher heart rate. Moreover, an activated sympathetic nervous system was associated with an increased mortality. An integrated physiological explanation of these findings could lead to the following interpretation. To compensate for a diminished stroke volume, heart rate will increase consequent on stimulation of the sympathetic nervous system. The elevated heart rate that co-occurs with a lower cardiac index fits a systemic adaptation to cardiac dysfunction. Thus, in the populations of older people that we have studied, a lower systolic blood pressure will likely mark imminent heart failure.

The observational data that are presented in this thesis showed that high blood pressure (both systolic and diastolic) was not related with excess morbidity and mortality. On the other hand, low blood pressure was related with excess

morbidity and mortality. As earlier stated, it is difficult to imagine that there is a certain age after which high blood pressure is beneficial instead of harmful. However, if low blood pressure is the result of a decreased cardiac output it could facilitate general hypoperfusion and hence explain the hazardous effect of low blood pressure at old age. Mean blood pressure rises with age and systolic blood pressure continues to rise whereas from the fifth and sixth decade of live diastolic blood pressure tends to lower.[12,13] This phenomenon is explained by a stiffer vascular system, particularly of the aorta. It is logical that in light of generalised atherosclerosis and increased vascular resistance, blood pressure raises to compensate for a decline in perfusion of vital organs. In an aging population, the prevalence of generalised atherosclerosis will be higher and therefore the risk of hypoperfusion will be increased. The recently published HYVET trial, that had positive results of treating high blood pressure in persons above 80 years old, is at first sight incongruent with our hypothesis. [14] However, the participants in the HYVET trial had considerably less cardiovascular disease (12%) when compared to the general population of the same age [60%, Chapter 2, this thesis]. Additionally, the mortality risk was considerably less then expected for that age group. Here I put forward the hypothesis that it was the healthiest people that were recruited into the HYVET trial for whom a benefit has been proven. This fits with the original inclusion criterion to exclude people with isolated hypertension that results of arterial stiffening and atherosclerosis. At older age this is the most common form of hypertension. Therefore, the results support treatment of people over the age of eighty that do not suffer from significant cardiovascular disease. It is however, difficult to generalize these results to older people in the population at large amongst which the presence of generalised atherosclerosis is the rule rather than the exception.

It is tempting to speculate how to select the people at old age who will benefit from the treatment of high blood pressure. Most persons will not fulfil the inclusion criteria of the HYVET, especially persons with a high cardiovascular risk. This being the case, what selection criterion should be used to select a healthy elder person? Most likely those with a high blood pressure concordant with a normal cardiac output should be treated rigorously. Alternative those with a high blood pressure concordant with a low cardiac output should not be treated. Pulse wave velocity could be of value as well. A higher pulse wave velocity reflects a

stiffer vascular tree and therefore a higher risk of hypoperfusion when high blood pressure is being lowered. Once treatment is started, the following question is to what extent blood pressure should be lowered. What are the treatment goals? The international guidelines on treatment of hypertension propose to lower the blood pressure to the lowest possible values, but in any case systolic blood pressure should be lower then 140 mmHg. If these treatment goals would also suit the older population we should institute a far more aggressive treatment than is currently applied. But negative outcomes of intensive treatment of high blood pressure have been observed among middle-aged people with severe vascular disease. [15] In an aged population, it is expected that the hazardous effects of aggressive treatment of high blood pressure will be even more pronounced.
As reported in the HYVET study, mortality risk from stroke was considerably lower in the treated versus placebo group. As stroke is a major risk factor for cognitive decline one should expect in the treated group positive results for maintaining cognition. Remarkably, there was no benefit on cognition in the participants with versus those without treatment for hypertension. [16] Though the follow-up might have been to short to reveal an effect on cognition there could be an alternative explanation. In line with our hypothesis it could very well be that active treatment, in this apparently healthy cohort, induced cerebral hypoperfusion. The beneficial effect of the reduced stroke incidence might have been traded off with cerebral hypoperfusion, with as a result a negligible effect on cognition.

In conclusion, the population-based reports indicating lower mortality and morbidity risks in association with high blood pressure in the very old are robust and cannot be ignored. [1-9] The results of interventional trials, including the recent HYVET trial, provide a solid body of evidence also.[14] This thesis supports the notion that clinicians should not base treatment of high blood pressure in older people on cut-off levels only. Clinicians have to make a decision whether high blood pressure in a particular patient is appropriate or not. My hypothesis is that high blood pressure concordant with a low cardiac output should not be treated in contrast with high blood pressure concordant with a normal/high cardiac output. According the Hippocratic Oath, clinicians have to prescribe medication for the good of their patients according their best ability and judgment without

doing harm. For the time being, treatment of high blood pressure in the very old is a clinical challenge with little general rules and highly individualized. It goes without saying that, future randomised controlled trials should focus on the outcomes of blood pressure lowering stratified on levels of cardiac output and or generalized atherosclerotic burden.

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